REMARKS

As an initial matter, Applicants' representative would like to thank the Examiner for the courtesy of extending a telephone interview with Applicants' Representative on March 16, 2010. During the interview, Applicants' the differences between the pending claims and the prior art documents were discussed. Specifically, Applicants' representative explained to the Examiner that the Dorval et al. document is directed to only protein A, and not the whole *Staphylococcus aureus* bacterium. As for the Hanke document, it does not teach or suggest the use of a whole *Staphylococcus aureus* bacterium as a control antigen immobilized on a solid support as recited in the present claims. Advantages of *Staphylococcus aureus* bacterium were also discussed. Applicants' representative also pointed out to the Examiner that there is nothing in either the Dorval et al. document or the Hanke document that teaches or suggests a detection substance that is an immunoglobulin which is raised against any kind of human immunoglobulin but does not react with protein A as recited in the present claims. In addition, Applicants' representative also pointed out to the Examiner that the use of goat and chicken antihuman immunoglobulins as recited in claim 17 has advantageous properties that are neither

In view of the above, in response to the Office Action dated June 23, 2009, Applicants respectfully submit the Remarks, and reconsideration is respectfully requested. Claims 1-14 have been canceled, and claims 15-25 remain in the application.

Amendment to Claims 15, 22 and 25

Applicants respectfully submit that claims 15, 22 and 25 have been amended to correct a typographical error. Specifically the recitation "the reaction product" has

been changed to “a reaction product” in claim 15.

This claim has been amended to remove improper use of an antecedent to conform to U.S. practice as suggested by the Examiner.

In addition, the bacterium *Staphylococcus aureus* and genuses *Rickettsia, Coxiella, Bartonella,Tropheryma, Ehrlichia, Chlamydia, Mycoplasma, Treponema, Borrelia,* and Leptospira are now italictize to conform with U.S. pratice.

Support for these amended claims can be found throughout the specification, particularly in the original claims and in the example. No new matter has been added. Hence, Applicants respectfully request consideration and entry of these claims.

The present invention

Applicants respectfully submit that the present invention is directed to an in vitro serological diagnosis method for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested.

The method of the present invention comprises (a) depositing on a solid substrate a first antigen Ag_1 comprising a whole *Staphylococcus aureus* bacterium which comprises protein A and at least one second antigen Ag_2, wherein said second antigen Ag_2 is an infectious microbial agent; (b) contacting said first antigen Ag_1 and said at least one second antigen Ag_2 with a sample to be tested causing said first antigen Ag_1 and said at least one second Ag_2 to react with a sample to be tested; (c) detecting whether a human immunoglobulin Ac_1 in said human serum reacts with said first antigen Ag_1 by causing a reaction product Ag_1-Ac_1 to react with a detection substance; and (d) providing a controlled sample containing a human serum to be tested for detecting whether said human immunoglobulin react with said

first antigen.

The detection substance of the present invention reacts with said human immunoglobulin and not with said first antigen (Ag_1), and the reaction product of Ag_1-Ac_1 is formed from the reaction of said human immunoglobulin Ac_1 and said first antigen Ag_1;

In addition, the detection substance of the present invention is a secondary detection antibody Ac_2 which is a labeled anti-human immunoglobulin which does not react with protein A and is labeled by fluorescent marking.

Summary of the Office Action

In the Office Action, claims 15, 19-21 and 24-25 have been rejected under 35 USC § 103 (a) for being unpatentable over Dorval et al. (US Patent No. 5,561,045) in view of Hanke (DE 100 00322A1). In addition, claims 22 and 23 have been rejected under 35 USC § 103 (a) for being unpatentable over Dorval et al. (US Patent No. 5,561,045) and Hanke (DE 100 00322A1) in view of La Scola et al. (Journal of Clinical Microbology, 1996; 34(9): 2270-2274). Finally, claims 15, 17 and 19-25 have been rejected under 35 USC § 112, 2nd paragraph for being indefinite.

First Rejection under 35 USC § 103

Claims 15, 19-21 and 24-25 have been rejected under 35 USC § 103 (a) for being unpatentable over Dorval et al. (US Patent No. 5,561,045) in view of Hanke (DE 100 00322A1). Applicants respectfully traverse.

Applicants respectfully submit that the Dorval et al. document is directed to only protein A, and not the whole *Staphylococcus aureus* bacterium. As for the Hanke document, Applicants respectfully submit that it does not teach or suggest the

use of a whole *Staphylococcus aureus* bacterium as a control antigen immobilized on a solid support as recited in the present claims.

Applicants also respectfully submit that the use of the whole *Staphylococcus aureus* bacterium is advantageous because:

- it is a corpuscular antigen control which is easier and relieable to adsorb onto a solid substrate when deposited thereon; and
- the detection by visualisation of a corpuscular control agent is much more reliable and easier to detect than the visualization of an immunological reaction between an immunoglobulin and a purified protein adsorbed on a solid substrate, especially with a fluorescent marking.

Applicants also respectfully submit that there is nothing in either the Dorval et al. document or the Hanke document that teaches or suggests a detection substance that is an immunoglobulin which is raised against any kind of human immunoglobulin but does not react with protein A as recited in the present claims.

In addition, Applicants respectfully submit that the use of goat and chicken antihuman immunoglobulins, as recited in claim 17, has advantageous properties that are neither taught nor disclosed in the prior art documents. These advantageous properties include the ability of not reacting with protein A.

In view of the above, Applicants respectfully submit that the present invention as recited in the pending claims are neither taught nor suggested by Dorval et al. alone or in combination with Hanke. There is nothing, in HANKE and/or DORVAL documents, that teaches or suggests the use of the entire or whole Staphylococcus

aureus bacterium as claimed in present invention.

Applicants further respectfully submit that there is nothing, in HANKE and/or in DORVAL documents, that teaches or suggests that the claimed detection substance is an immunoglobulin which is raised against any kind of human immunoglobulin (Iga + IgM + IgG + IgE+ etc) and which is raised so that it does not react with protein A.

On page 8, lines 1-10, of the last Office Action, the Examiner alleges that a detection agent which is a "labeled antihuman immunoglobulin which does not react with protein A" is taught by Dorval et al. because Dorval et al. teach that" "the presence of IgM and/or IgA, as well as IgG (are) determined without unwanted binding between any species in the detection reagent and any analyte or between any two species in the detection reagent".

Applicants respectfully request reconsideration and withdrawal of this allegation because it appears that the Examiner has failed to take into account the preceding submission of Applicants, wherein it was explained that, in Dorval et al. a blocking agent is used to prevent interaction between protein A and anti-Iga IgG or anti-IgM IgG. Please see column 4, lines 13-15 of Dorval et al. where Dorval clearly discloses that there is an evidence that the concerned anti-IgA IgG and anti-IgM IgG have not been raised so that they don't react with protein A.

As already stated in the previously Amendment filed on September 23, 2009, indigo serves both as a label and a blocking agent, blocking the binding site on each anti-IgA IgG and anti-IgM IgG with protein A.

The use of an antihuman immunoglobulin as detection substance, according to the present invention, is advantageous in respect to the use of a labeled protein A as disclosed in Dorval et al., because, according to the present invention, a second

immobilized antigen Ag_2 must be detected and the labeled protein A would be unable to detect anti-Ag_2 IgM in the event where the presence of such anti-Ag_2 IgM immunoglobulin would be tested (protein A would be able to bind only to anti-Ag_2 IgG).

It is respectfully submit that besides using protein A as a detection substance in the process of the invention is less relieable than using an antihuman immunoglobulin as a detection substance for the further reason that for detecting the complex Ag_1-human IgG fixed to the solid support (wherein Ag_1 = Staphylococcus bascteria), the labeled protein A would enter in competition with the protein A of the Staphylococcus bacteria immobilized onto the solid support. Therefore, protein A (as a detection substance) would react less efficiently with the human immunoglobulin bound to the Staphylococcus bacteria immobilized onto solid support. Accordingly, antihuman immunoglobulins are preferred as a detection substance because they bind to human immunoglobulin through a different binding site than the binding site of human IgG with protein A of Staphylococcus bacteria.

Applicants respectfully submit that Dorval et al. is directed to a method and kit that is different from the claimed invention as recited above and acknowledged by the Examiner.

Applicants respectfully submit that the Dorval et al. document is directed to a method for simultaneously detecting immunoglobulins including IgG, IgA and/or IgM in a single test assay so that if any of these immunoglobulins have been produced in response to a particular infection agent, such production could be detected which is different from the claimed invention.

In the Office Action, the Examiner alleges that Figure 1A-1F of Dorval et al. teach a solid support with the first antigen containing protein A, a second microbial antigen, the addition of the detection agent which is labeled antihuman immunoglobulin which does not react with protein A. Applicants respectfully submit that this allegation is not supported by the Dorval et al. document. Applicants respectfully submit that this allegation this is not taught nor suggested by the Dorval et al. document for the reasons presented below and as set forth in columns 10 and 11 of the Doral et al. document. Applicants respectfully submit that in contradiction to the Examiner's allegation, Figures 1A-1F clearly state that a labeled protein A is used as a detecting substance. Column 11, lines 18-19 of the Dorval et al. document clearly states that "according to the assay, the detection reagent includes protein A (36) coupled to a hydrophobic label, specifically indigo."

Applicants respectfully submit that although protein A is immobilized on a support solid, this immobilized protein A reacts with IgG of all specificities present in the sample (see figure 1B) and the detection substance between immobilized protein A and IgG (see figure 1C) is protein A labeled with indigo (36) to detect the reaction product PA-IgG. Applicants also respectfully submit that according to the Dorval et al. document, labeled protein A is used in combination with two other detection reagents as shown in Figures 1C, and as recited in column 11, line 21: "the reagent also includes anti-IgA-IgG 38…and anti-IgM-IgG 40…indigo is coupled to each of anti-IgA-IgG 38 and anti-IgM-IgG 40…".

Applicants respectfully submit that the Dorval et al. document is directed to detecting simultaneously immunoglobulins including IgG, IgA and/or IgM in a single test assay so that if any of these imunoglobulins have been produced in response to

a particular infection agent, such production could be detected. Applicants respectfully submit that according to the Dorval et al. document, a labeled protein A is used to determine the presence of IgG while labeled anti-IgA-IgG or labeled anti-IgM-IgG is used to determine the presence of IgA or, respectively, IgM. However, when such agents are used together, the labeled protein A can bind to the labeled anti-IgA-IgG and anti-IgM-IgG. (See column 5, lines 50-62 of the Dorval et al. document).

Applicants respectfully submit that column 10, lines 24, 25, 26 of the Dorval et al. document clearly recites that "the invention is useful whenever it is desirable to prevent the interaction of two detection reagents with one another". According to Dorval et al., a blocking agent is used to prevent interaction between the two detection reagents, namely protein A and anti-IgA-IgG or anti-IgM-IgG. Applicants also respectfully submit that column 10, lines 2-3 of the Dorval et al. document clearly recites that "preferably, these labeled immunoglobulins are blocked with the label itself and the detection reagent includes labeled protein A, labeled and blocked anti-IgA-IgG and labeled and blocked ani-IgM-IgG. According to the assay of Dorval et al., the detection reagent includes protein A 36 coupled to a hydrophobic label, specifically indigo, which binds to IgG bound to protein A at area 12 of surface 10 and to IgG bound to HIV at area 16 of surface 10. The reagent also includes anti-IgA-IgG 38 which binds to IgA bound to IgV at area 16 of surface 10 and anti-IgM-IgG 40 which binds to IgM bound to HIV at area 16 of surface 100. More specifically, as specified in column 11, lines 24-27, "indigo (the label) is coupled to each of anti-IgA-IgG 38 and anti-IgM-IgG 40, serving both as a label and a blocking agent blocking the biding site of each from interaction with a protein A."

In view of the above, Applicants respectfully submit that the invention of Dorval et al. is different from the claimed invention. Applicants respectfully submit that the present invention is directed to a detection substance that does not comprise a labeled protein A but an anti human immunoglobulin that does not reacting with protein A as recited in the present claims. Applicants also respectfully submit that there is nothing in the Dorval et al. document that teaches or suggests that the protein A can be used as a control antigen for determining whether or not a negative serum sample is due to the absence of reaction with a serum, let alone a controlled sample to be tested containing a human serum. In addition, Applicants respectfully submit that in the method of Dorval et al., only protein A is used instead of the entire Staphylococcus aureus bacterium as recited in the claims of the present invention.

As for the Hanke document, Applicants respectfully submit that Hanke neither teaches nor suggests the claimed invention. The Hanke document relates to immune-whether-guide-mature. Hanke does not teach or suggest using the entire Staphylococcus aureus as a control antigen immobilized on a solid support to detect antibodies specific to an infectious microbial agent as claimed in the present invention.

Applicants respectfully submit that the use of the entire Staphylococcus aureus bacteria in the present invention is advantageous because (1) it is a corpuscular antigen control which is easier and reliable to adsorb onto a solid substrate when deposited thereon; and (2) the detection by visualisation of a corpuscular control agent is much more reliable and easier to detect than the visualisation of an immunological reaction between an immunoglobulin and a purified protein adsorbed on a solid substrate, especially with a fluorescent marking.

Applicants respectfully submit that in view of the above, there is nothing in the Hanke document that teaches or suggests the claims of the present invention.

Again, Applicants respectfully submit that neither the Dorval et al. document nor the Hanke document teaches or suggests the use of the entire Staphylococcus aureus bacterium to detect the presence of antibodies specific to an infectious microbial agent as recited in the claims of the present invention. In addition, neither the Dorval et al. document or the Hanke document teaches or suggests a method or kit for detecting whether the tested sample contains a human serum by detecting whether said detection substance consisting in an anti human immunoglobulin react or not with a human immunoglobulin-first antigen reaction product as reacted with the said detection substance as claimed in the present invention.

In view of all the differences and advantages of the claimed present invention discussed above, Applicants respectfully submit that one of ordinary skill in the art would be motivated to utilize the teaching of Dorval et al. either alone or in combination with Hanke at the time of the invention was invented to modify the method taught by Dorval et al. to arrive at the claimed invention in order to provide an easy control test of the presence of a human serum in the sample tested in the serological diagnosis method.

Hence, Applicants respectfully request reconsideration and withdrawal of this rejection.

Second Rejection under 35 USC § 103

In addition, claims 22 and 23 have been rejected under 35 USC § 103 (a) for being unpatentable over Dorval et al. (US Patent No. 5,561,045) and Hanke (DE 100 00322A1) in view of La Scola et al. (Journal of Clinical Microbology, 1996; 34(9):

2270-2274). Applicants respectfully traverse.

As discussed above, Applicants respectfully submit that neither the Dorval et al. document nor the Hanke document teaches or suggests the use of the entire *Staphylococcus aureus* bacterium to detect the presence of antibodies specific to an infectious microbial agent as recited in the claims of the present invention.

In addition, neither the Dorval et al. document or the Hanke document teaches or suggests a method or kit for detecting whether the tested sample contains a human serum by detecting whether said detection substance consisting in an anti human immunoglobulin react or not with a human immunoglobulin-first antigen reaction product as reacted with the said detection substance as claimed in the present invention.

As for the La Scola et al. document, this document cannot be used to cure the deficiencies of the Dorval et al. document.

Applicants respectfully submit that La Scola et al. disclose serological cross-reactions between *Bartonella quintana, Bartonella henselae,* and *Coxiella burnetti.*

Applicants respectfully submit that La Scola et al. neither teach nor suggest a method or kit for detecting the presence of antibodies specific to an infectious microbial agent in a sample to be tested using a whole *Staphylococcus aureus* as recited in the claims of the present invention. Further, the La Scola et al. document neither teaches nor suggests a method comprising (a) depositing on a solid substrate a first antigen Ag_1 comprising a whole Staphylococcus aureus bacterium and at least one second antigen Ag_2; (b) contacting said first antigen Ag_1 and said at least one second antigen Ag_2 with a sample to be tested causing said first antigen Ag_1 and said at least one second Ag_2 to react with a sample to be tested; (c)

detecting whether a human immunoglobulin Ac_1 in said human serum reacts with said first antigen Ag_1 by causing the reaction product Ag_1-Ac_1 to react with a detection substance; and (d) providing a controlled sample containing a human serum to be tested for detecting whether said human immunoglobulin react with said detection substance has reacted with the reaction product as recited in the claims of the present invention.

Therefore, one of ordinary skill in the art would not be motivated to combine the teaching of Dorval et al. with the teaching of Hanke and La Scola et al. to make the present invention.

In view of the above, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 USC § 112, 2nd paragraph

Claims 15, 17 and 19-25 have been rejected under 35 USC § 112, 2nd paragraph for being indefinite.

Applicants respectfully submit that claims 20, 22 and 24 have been amended.

Applicants also respectfully submit that claims 20, 22 and 24 have been amended to clarify the claimed subject matter of the present invention. Specifically, claims 20, 22 and 24 have been amended as suggested by the Examiner under Item 5 at page 3 of the Office Action. These claims have been amended to properly recite a Markush group to conform to U.S. practice as suggested by the Examiner. Also, claim 24 has been amended to replace the abbreviations of H.I.V. and C.M.V. with human immunodeficiency virus and cytomegavirus as suggested by the Examiner to conform to U.S. practice. Support for these amended claims can be found throughout the specification.

No new matter has been added. Hence, Applicants respectfully request consideration and entry of these claims.

CONCLUSION

In light of the foregoing Remarks, Applicants respectfully submit that the application is now in condition for examination.

Should any minor matter remain, or should the Examiner feel that an interview would expedite the prosecution of this application, the Examiner is invited to call the undersigned to arrange such.

To the extent necessary, Applicant petitions for an extension of time under 37 CFR 1.136. Please charge any shortage in the fees due in connection with the filing of this paper, including extension of time fees, to the deposit account of Antonelli, Terry, Stout & Kraus, LLP, Deposit Account No. 01-2135 (Case: 935.44544X00), and please credit any excess fees to such deposit account.

Respectfully submitted,

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